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(54) Title: PRODUCTION OF GLYCOSIDES, ESPECIALLY OF STEROIDAL GLYCOSIDES

(57) Abstract

For a production of glycosides, especially of steroidal glycosides, molecular iodine is used as a reaction catalyst, wherein an alcohol and/or phenol, especially a hydroxy-steroid, is glycosylated, such that the glycosylation is performed in one single step and without extensive laboratory measures, such as nitrogen gassing and/or extremely high temperatures, and the avoidance of halogenated glycosides and toxic reaction catalysts, such as for example Ag_2O, Ag_2CO_3, $PbCO_3$, $Hg(CN)_2$, etc. and the avoidance of the formation of ortho esters. The steroidal glycoside obtained in this way possesses valuable pharmacological properties, in particular it exhibits a cell-destruction activity free of side effects on malignant cells and a drive-enhancing activity as well.

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Production of glycosides, especially of steroidal glycosides

Field of the invention

This invention relates to a method for the production of a glycoside by glycosylation of an alcohol and/or a phenol, preferably a hydroxy-steroid, as well as a steroidal glycoside and a medicament containing the same.

An object of the invention is a method for the production of a glycoside and the steroidal glycoside according to the invention as well as the provision thereof as a therapeutically-active substance, medicaments based on this steroidal glycoside for control or prevention of diseases, especially for treatment of cancer diseases, geriatric diseases, states of hyperactivity and/or states of diminished activity, or for the manufacture of a medicament for the treatment of cancer diseases, geriatric diseases, states of hyperactivity and/or states of diminished activity.

Background of the invention

The glycosylation of alcohols and/or phenols and particularly that of hydroxy-steroids is known per se; however, often there arise undesired ortho esters as e.g. described in Chemical Abstracts, Vol. 105, 1986, 172882s. A method which allows the content of this undesired ortho ester to be decreased is disclosed in Chemical Abstracts, Vol. 104, 1986, 22511g (Liebigs Ann. Chem. 1986, 717-730), however, this method does not allow the complete avoidance of the formation of ortho esters, and, further, a pivaloylglucopyranosylbromide must be used, wherein the pivaloyl groups function as protecting groups to suppress the formation of ortho esters. The reaction of the glycoside with the steroid proceeds by means of silver oxide or silver carbonate catalysts.

The use of α-halogen-tetraacetylglucose which is commonly used for the glycosylation of steroids, especially that of

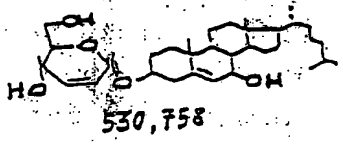
cholesterol, necessitates the use of expensive and/or toxic reaction catalysts, such as Ag_2O, Ag_2CO_3, $PbCO_3$, $Hg(CN)_2$ etc., which frequently prohibits its technical application on a larger scale. Furthermore, these glycosylation procedures generally constitute multistage processes which also lead to the production of α- as well as to ß-glycosylation.

This invention solves the problem of providing a novel glycoside, especially a steroidal glycoside, for pharmacological application. The glycosylation for the production thereof proceeds in one step and without extensive laboratory measures, such as nitrogen gassing and/or low temperatures, and avoids halogenated glycosides and the utilization of toxic reaction catalysts, such as for example Ag_2O, Ag_2CO_3, $PbCO_3$, $Hg(CN)_2$ etc. and avoids the formation of ortho esters.

Summary of the invention

It has been surprisingly found that members selected from the group consisting of alcohols and phenols and preferably hydroxy-steroids, wherein hydroxy-steroids are to be understood as members selected from the group consisting of steroidal alcohols and steroidal phenols, can be reacted with a glycosidic vinyl ether in the presence of molecular iodine as a catalyst in one step to yield a glycoside in high yield. Thus there is no need for expensive and toxic reagents in this reaction step. Furthermore, a steroidal glycoside has been found which is obtainable by this method and which can be employed as a highly efficient medicament, especially as an anti-cancer agent, in geriatric medicine, as a sedative and/or activity-enhancing agent. Method of treating symptoms of at least one member selected from the group consisting of cancer disease, geriatric disease, states of restlessness and states of weakness, comprising administering to a patient suffering from cancer disease, geriatric disease, states of restlessness as states of weakness a pharmaceutical effective amount of a

compound of the formula:



In the accompanying drawings with reference to preferred examples of the invention:

Diagram 1 is an infrared spectrum of the glucal used in the reaction of Example 1;

Diagram 2 is an infrared spectrum of the glycosylation product of Example 1;

Diagram 3 is an NMR-sectrum of the same glycosylation product of example 1;

Diagram 4 and 5 are the IR-spectrum and the NMR-spectrum, respectively of the ketone product of example 2;

Diagrams 6 and 7 are the IR-spectrum and the NMR-spectrum, respectively, of the 7ß-OH Cholesterol product of example 3; and

Diagram 8 is a plot showing the tumor cell groth inhibition by selected concentrations of 7ß-OH cholesterol in cell culture field.

Detailed description of the invention

According to one preferred embodiment of the method of the invention, an oxysteryl compound, preferably a 3ß-ol sterol compound, more preferably a delta^5-3ß-ol steroid compound such as a cholesterol, (e.g., delta^5-cholesten-3ß-ol) is glycosylated by reaction with 3,4,6-tri-O-acetyl-D-glucal in an inert solvent in the presence of molecular iodine as a

catalyst. The reaction is achieved in one single step and in high yield. Thus a double bond which is strongly hindered by the C_4, C_6-acetyl groups and thus being inert, is introduced between C_2=C_3 of the glycosidic part of the molecule, whereby the delta^5 double bond of the perhydro-cyclopentano-phenanthrene skeleton remains unchanged. Furthermore, the reaction of the unsaturated glycoside which is obtained as an intermediate to functional cholesterol derivatives is performed according to the method of this invention. Functional groups can be introduced into the perhydro-cyclopentano-phenanthrene skeleton of said unsaturated acetoglycoside, wherein the α-bond of the acetoglycoside at the same time functions as a protecting group for the original OH-group at C_3 of the phenanthrene skeleton.

In contrast to the analytical procedure for the iodometric assay of vinyl ethers by ionized iodine in alcohol with formation of the corresponding iodoacetals according to S. Siggia and R. L. Edsberg, Ind. Eng. Chem. Anal. 20, 762 (1948), thereby using ionized iodine in the reaction, the method according to this invention makes use of iodine being molecularly dissolved in inert solvents such as for example CH_2Cl_2 dichloromethane, $CHCl_3$ chloroform, CCl_4 carbon tetrachloride, $C_6H_4(CH_3)_2$ xylene, $C_6H_3(CH_3)_3$ mesitylene, $C_6H_5CH(CH_3)_2$ cymene, C_6H_{12} cyclohexane and methyl derivatives thereof, as well as ligroin, petroleum ether and saturated hydrocarbons, such as for example n-pentane or n-heptane, preferably C_6H_6 benzene or $C_6H_5CH_3$ toluene.

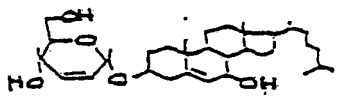
The method according to the invention is applicable to the glycosylation of hydroxy compounds in general and broadly, e.g. all compounds with free alkoholic HO-groups as for example prim., sec., or tert. alcoholic groups, aliphatic, aliphatic-aromatic or aromatic. Preferred hydroxy compounds for glycosylation comprise cholesterols, bile salts, steroid hormones, and vitamin D compounds and precursors as described in Stryer's Biochemistry, 3rd Ed. pp. 559-570, Freeman and Company, New York, 1988, incorporated herewith by reference.

Specifically steroid derivative such as: Cholic acid and derivatives, 25-hydroxy-cholesterol, 25-hydroxy-calciferol, Pregnenolone, 17α-hydroxy-pregnenolone, 17α-hydroxy-progesterone, 11-desoxy-corticosteron, 11-desoxy-cortisol, corticosterone, cortisol, cortisone, androsterone, testosterone, estrone, 17β-estradiol, estratriol-3, 16α, 17β, 3α, 5β-tetrahydro-corticosterone, urocortisol and allocortolone preferably cyclopentano-perhydrophenanthrene compounds having the delta^5-3β-OH steryl moity.

The method according to this invention is preferably directed to the reaction of the vinyl ether of 3,4,6-tri-O-acetyl-D-glucal with delta^5-cholesten-3β-ol with a catalytic amount of molecularly dissolved iodine in one of the aforementioned solvents, thereby introducing a double bond between C-atoms 2 and 3 while eliminating the acetyl group sited at C_3, instead of introducing an iodine atom at C_2 in the glycosidic part of the resulting cholesterylglycoside. The iodine being utilized in a catalytic amount is quantitatively titrated back by, e.g., 0.1 N aqueous sodium thiosulphate ($Na_2S_2O_3$). This reaction is followed by IR-spectroscopy, and is complete only when the peak of the glucal at 1650 cm^{-1} has disappeared.

In a further step, the product obtained by the foregoing reaction can be converted by oxidation of the steroidal part into the α-glycosylated 7-keto-cholesterol. The oxidation is accomplished with an oxidizing agent, which preferably contains chromium, with pyridine-chromium-trioxide $(C_5H_5N)_2CrO_3$ or pyridine-chlorochromate $(C_5H_5NHCrO_3)Cl$ being preferred and t-butyl chromate being especially preferred. The inert glycosidic double bond between C_2=C_3 thereby remains intact as it is shielded by the C_6, C_4 acetyl groups The reduction of this 7-ketone with suitable, preferably complex metal hydrides, such as e.g. $NaBH_4$, $LiBH_4$, KBH_4 and preferably $LiAlH_4$, leads, after e.g. chromatographic separation of the C_7 α-hydroxy derivative, the 3β-O-(4,6-dihydroxy-2,3-dideoxy-D-erythro-α-2-hexyl)-delta^5-cholesten-7α-ol, with a suitable solvent mixture, preferably a mixture consisting of dichloromethane 1 : acetone

1, to the steroidal glycoside according to this invention, to the 3ß-O-(4,6-dihydroxy-2,3-dideoxy-D-erythro-α-2-hexyl)-delta^5-cholesten-7ß-ol of formula



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This compound posesses valuable pharmacological properties, in particular it exhibits a cell-destructive activity - free of side effects - on malignant cells and a drive-enhancing activity as well as a tranquilizing activity. The steroidal component, the delta^5-cholesten-3ß,7ß-diol, constitutes an own steroid of the thymus gland being a native signal substance of the cellulary immune response which previously has been successfully employed in the treatment (free of side effects) of cancer diseases of all phenotypes. Whereas the delta^5-cholesten-3ß,7α-diol is formed in the liver as the first degradation product of cholesterol and posesses no physiological activity; the delta^5-cholesten-3ß,7ß-diol is formed in the thymus gland of all mammals as a universal signal substance of their own immune defence. It owes its activity, which is solely directed to malignant cell surfaces, to the fact that it is bound unspecifically by LDL (low density lipoproteins), which are responsible for the essential transport of cholesterol into the interior of the cell and for the construction of the cell membranes, and that it is transferred by the latter ones, presumably via the NK-cells (natural killer cells) onto the cell membranes of deviated tissue, particularly onto cancerous tissue. As, in contrast to normal soma cells, the receptors of LDL on the surface of cancer cells are degeneratively modified, having undergone a modification of their spatial structure, the 7ß-hydroxy-cholesterol effects a blocking of the receptors modified in this way. This is comparable to the plug of a bottle, wherein the cancer cell is cut off from the supply of the vital cholesterol. Hence it follows that an osmotic excess pressure

builds up in the interior of the cancer cell, finally leading to the colloid-osmotic induced rupture of the cancer cell. The cytoplasma of the cancer cell is then forced out. Thus the cancer cell ceases to exist (Diagram 8).

This method, lasting only for about 8 to 10 minutes, has been investigated microscopically and recorded by Alex Matter (Microcinematographic and electron microscopic analysis of target cell lysis induced by cytotoxic T lymphocytes, Immunology 36, 179 - 190 (1979)). No statement concerning the chemical nature of the body's own active substance is made.

7ß-Hydroxy-cholesterol was detected, together with progesterone, 11ß-hydroxy-progesterone, cortexone and 7-keto-cholesterol, in thymus extracts for the first time in 1976 by Klemke (unpublished results), using the antimony trichloride reaction for stenols, IR-spectroscopy and NMR-spectroscopy. Lateron Reisch and El Shakary, Scientia Pharmaceutica 50, 75-78 (1982) confirmed these findings after the group of J. P. Beck in Strasbourg, J. Chem. Res. (S) 1977, 217 - 219, had previously found that 7ß-hydroxy-cholesterol constitutes the antiproliferatory active substance of a very ancient Chinese drug, the Bombyx cum Botryte, a silkworm (Bombyx mori) having been killed by a microscopic fungus (Botrytis bassiana Balls). Further details have been published in Vol. 32/ TUMOSTERON "Schriftenreihe Krebsgeschehen" of the Verlag für Medizin, Heidelberg 1986. The delta^5-cholesten-3ß,7ß-diol was recognized as a biochemical signal compound of the body's own immune defence system. In contrast to the conventional cytotoxic treatment of cancer diseases this turns out to be completely non-toxic and to be capable to eliminating cancer cells of any phenotype and not affecting healthy cells.

It is true that a glycosylated cholesterol is known from Chemical Abstracts Vol. 97, 1982 6734s, which possibly might constitute a neoplastic inhibitor; however this molecule has in its glycosidic moiety at C_2 a bulky 2-chloroethyl-amino-carboxamido group and at C_7 of the cholesterol the 7ß-hydroxy

group is lacking. This latter group, however, is important for the activity of the steroidal glycoside according to the invention, as this steric array is also important for the respective cellular receptor.

In the treatment method of the invention the compound according to the invention can be used as a medicament in the form of pharmaceutical preparations comprising this compound in admixture with a pharmaceutically acceptable carrier. One skilled in the art of preparing formulations can readily select the proper form and method of administration depending upon the particular characteristics of the compound selected, the disease state to be treated, the stage of disease, and other relevant circumstances. These preparations can be administrated orally, e.g. in the form of tablets, dragees, gelatin capsules, soft capsules, solutions, emulsions or suspensions or parenterally, e.g. in the form of injectable solutions or topically, e.g. in the form of cream. The compound can be administered alone or in the form of a pharmaceutical composition in combination with pharmaceutically acceptabel carriers, preservatives, solubilizers, stabilizers, humectants, emulsifiers, sweetening agents, dyes, scents, salts to modify the osmotic pressure, buffers, coating agents, antioxidants such as for example tocoquinones (tocopheroles), glutathione, cystein, ascorbic acid sodium salt etc.

The carriers mentioned above may constitute pharmaceutically inert anorganic or organic materials. Examples of carriers for tablets, capsules and hard gelatine capsules include lactose, maize-starch or derivatives thereof, talcum, stearic acid or salts thereof. Examples of carriers for soft gelatine capsules are vegetable oils, waxes, fats, semi-solid and liquid polyols. Examples of carriers for the manufacture of solutions or syrups include water, polyols, saccharose, inverted sugar and glucose. Examples of carriers for injectable solutions include water, alcohols, polyols, glycerol and vegetable oils. The pharmaceutical preparations may also comprise conventional pharmaceutical adjuvants such as preservatives, solubilizers,

stabilizers, humectants, emulsifiers, sweetening agents, dyes or scents, salts to modify the osmotic pressure, buffers, coating agents or antioxidants. They may also include other therapeutically valuable ingredients.

The pharmaceutical preparations may be manufactured by admixing the compound according to this invention, if desired in combination with other therapeutically valuable substances, with an acceptable pharmaceutical carrier and, if desired, with a pharmaceutical adjuvant, and transforming the admixture into the desired form for administration.

Dosages:

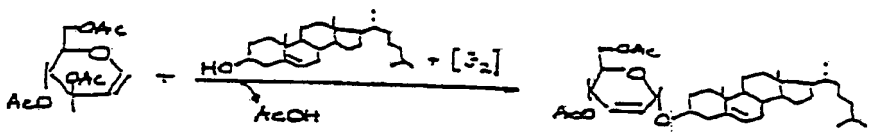
In the treatment of cancer a dosage of at most 80 mg per day, preferably 10 mg to 30 mg per day, more preferable 10 mg to 20 mg.

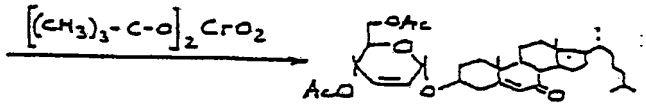
For the purpose of parenteral therapeutic administration, the compound of the present invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1 % of a compound of the invention, but may varied to be between 0.1 % and about 50 % of the weight thereof. The amount of this inventive compound presents in such compositions is such that suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 5 mg to 80 mg, more preferred 5 to 40 mg, most preferred 10 to 40 mg.

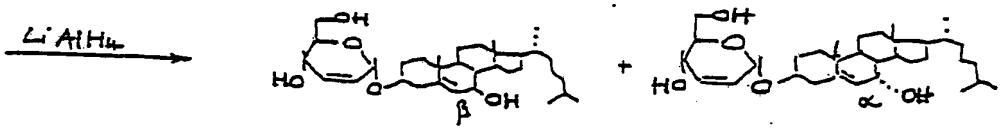
A therapeutically effective dose can be readily determined by the attending diagnosticians, as one skilled in the art, by the use of conventional techniques and by observing results obtained under analoguous circumstances. In determing the therapeutically effective dose, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammals, the size, age and general response of the individual patient; the particular compound

administered; the mode of administration; the biovailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances. A therapeutically effective amount of a compound according to the invention is expected to vary from about 0.07 mg per 1 kg of body weight per day (mg/kg/day) to about 1.25 mg/kg/day. Preferred amounts are expected to vary from about 0.15 mg/kg/day to about 0.3 mg/kg/day.

The reaction steps described subsequently are disposed as follows:

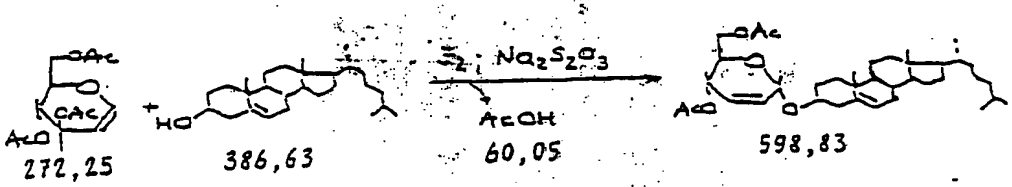






Example 1

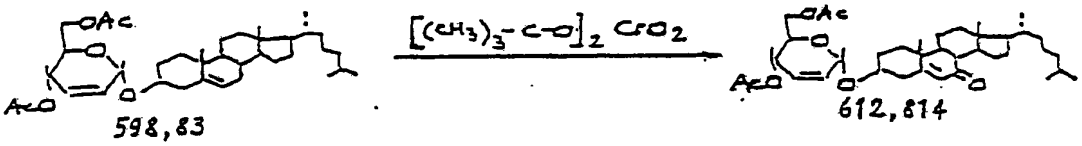
Preparation of
3ß-O-(4,6-O-acetyl-2,3-dideoxy-D-erythro-α-hexyl)-delta^5-cholestene



5.0 g (= 0.02 mole) molecular iodine were dissolved with stirring in 300 ml benzene in a 2-litre three-necked flask fitted with stirrer, reflux condenser and thermometer. To the wine-red solution thus obtained was added the solution of 27.2 g (= 0.10 mole) 3,4,6-tri-O-acetyl-D-glucal and 38.6 g (= 0.10 mole) delta^5-cholesten-3ß-ol in 700 ml of benzene. In the course of 2 hours the mixture was heated to 70-75 °C. The reaction was monitored by IR-spectroscopy; it was terminated only when the peak of the glucal at 1650 cm^{-1} (Diagram 1) has disappeared. The red colour of the reaction solution is not significant. After removal of the flask heater the reaction solution is rapidly cooled in a water-bath to about 20-30 °C. After transfer into a 2-litre separatory funnel the cooled wine-red reaction solution was extracted until complete discoloration with 500 ml + 10% of
0.1 N = 12.5 g + 10 % = 13.8 g aqueous solution of Na_2SO_4, washed twice with water, treated with activated carbon, dried over anhydrous Na_2SO_4 and the solvent is distilled off, finally in vacuo.
Crude yield: 58.3 g (= 97.4% th.).
The raw product is recrystallized from 2 litres of CH_3OH.
Yield: 56.95 g (= 95.1% th.)
Mp: 118-120 °C
IR-spectrum: Diagram 2
NMR-spectrum: Diagram 3

Example 2

Preparation of 3ß-O-(4,6-O-acetyl-2,3-dideoxy-D-erythro-α-2-hexyl)-delta^5-cholesten-7-one



In a 250 ml three-necked flask fitted with reflux condensor, dropping funnel, thermometer and magnetic stirrer 6.00 g (= 0.01 mole) of the unsaturated glycoside from Example 1 of mp 118-120 °C were dissolved in 45 ml of CCl_4 and heated to boiling (80 °C). In the course of 30 minutes the mixture of 10 ml Ac_2O (acetic anhydride) and 40 ml t-butyl chromate, prepared according to the Annex, was slowly added dropwise to the boiling solution and stirred for another 10 hours at the boiling point. After cooling, a solution of 6.0 g oxalic acid in 60 ml water was added dropwise in the course of 45 minutes at 5 °C to 10 °C in an ice-bath followed by 4.2 g solid oxalic acid. Stirring was then continued for another 2 hours. Thereafter separation took place in the separating funnel, the upper dark aqueous phase being extracted twice with CCl_4, the combined CCl_4-solutions extracted with water, saturated solution of $NaHCO_3$ and then with water again, in this order, and dried over Na_2SO_4. Finally the solution was discolored with activated carbon. After concentration in vacuo the straw-yellow residue was dissolved in 25 ml of a mixture consisting of cyclohexane 40 : ethyl acetate 10 : chloroform 1 and chromatographed on a silica gel column (diameter 2.5 cm; height 25 cm), charged with 60 g of silica gel 40 (Merck Article 10180) and the same solvent mixture.

Yield: Fraction 1: 1.8 g (= 30.1 % of theory) unchanged starting material.

Fraction 2: 4.2 g (= 68.5% of theory) 7-keto-compound

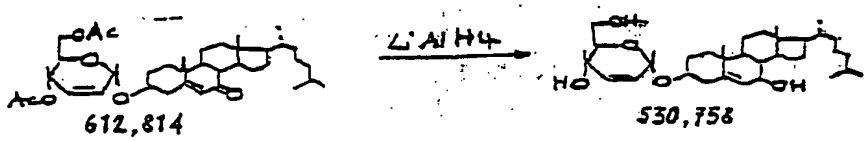
Mp: 113-115 °C
IR-spectrum: Diagram 4
NMR-spectrum: Diagram 5

Annex:
Preparation of t-butyl chromate

In a 500 ml beaker, 187.2 g (= 2.5 mole) t-butanol of mp 24.5 °C were warmed to 28 °C and melted. To this melt, 74 g (= 0.74 mole) of CrO_3 were added by using a thermometer as a stirring bar. In order to keep the reaction temperature below 30 °C, occasional cooling with ice-water was necessary. The liquid reaction product was diluted in a separating funnel with 520 ml of CCl_4 and left to stand overnight. This standing is important to allow clarification of the solution. The following morning, the upper dark layer was separated. The clear CCl_4-solution was dried with 50 g of anhydrous Na_2SO_4, filtered and the Na_2SO_4 washed with 320 ml of CCl_4. Thereafter, the combined CCl_4-solutions were concentrated to 400 ml in vacuo in a water-bath at a temperature of 40 °C to 45 °C, wherein excess t-butanol and CCl_4 were both distilled azeotropically. The solution thus obtained may be kept unchanged in the refrigerator at -1 °C for at least one month.

Example 3

Preparation of 3ß-O-(4,6-Hydroxy-2,3-dideoxy-D-erythro-α-2-hexyl)-delta^5-cholesten-7ß-ol



6.13 g (= 0.01 mole) of pure compound from Example 2 with mp 113-115 °C were dissolved by heating in 100 ml peroxide-free ether which has been dried with metallic sodium and cooled to room temperature. A solution of 0.8-1.0 g (= 0.021 mole) $LiAlH_4$ in 100 ml absolute ether was added to a 500 ml three-necked

flask with magnetic stirrer, reflux condensor and thermometer. The ethereal solution of the unsaturated aceto-7-keto-glucoside was then added dropwise with sufficient stirring such that the reaction temperature did not substantially exceed 20 °C, if possible. After addition had been terminated, which may take up to two hours, stirring was continued for another 2 hours.

Afterwards, the reaction mixture was cooled in ice-water and treated drop by drop with H_2O until all H_2 (conducted to the outlet of the hood by means of a tube) had evolved. H_2O-consumption was about 5.0 ml. On a larger scale, the use of $CH_3COOC_2H_5$ is recommended. In order to dissolve the $LiAlO_2$ formed, the solution was stirred with 16 ml of 10% H_2SO_4 and, after transfer to a 500 ml separating funnel, diluted with 100 ml of ether and shaken thoroughly. Thereby, the reaction product, which has separated as crystals, goes completely into solution. The acidic aqueous solution was extracted once with ether and the combined ethereal solutions washed with 100 ml of a saturated NaCl-solution in two portions of 50 ml each. After drying over anhydrous Na_2SO_4, the filtrate was kept in the refrigerator at -1 °C for 9 hours. The crystals thus obtained are collected by suction over a G4-suction filter and weighed.

Crude yield: 5.10 g (= 96.23% of theory)
mp: 165 -167 °C

This compound was dissolved in 25 ml of dioxane by heating and chromatographed on a column of silica gel (diameter 5.0 cm; height 70 cm) charged with 300 g of silica gel 40 (Merck Article 10180) using a solvent mixture consisting of dichloromethane 1 : acetone 1.

Yield:
Fraction 1: 0.35 g (= 6.8%) 7α-OH-compound, mp: 161-195 °C.
Fraction 2: 4.60 g (= 90.2%) 7ß-OH-compound, mp: 181-183 °C.
IR-spectrum: Diagram 6
NMR-spectrum: Diagram 7

Claims

1. Method for the production of a glycoside, comprising glycosylating at least one member selected from the group consisting of an alcohol and a phenol by reaction with a glycosidic vinyl ether in the presence of a catalytic amount of molecular iodine.

2. Method according to Claim 1, wherein said at least one member selected from the group consisting of an alcohol and a phenol is a hydroxy-steroid.

3. Method according to claim 2, wherein the hydroxy-steroid is delta^5-cholesten-3ß-ol and the glycosidic vinyl ether is 3,4,6-tri-O-acetyl-D-glucal.

4. Method according to claim 3, wherein the product formed by the glycosylation is 3ß-O-(4,6-O-diacetyl-2,3-dideoxy-D-erythro-α-2-hexyl)-delta^5-cholestene.

5. Method according to claim 4, further comprising oxidizing the 3ß-O-(4,6-O-diacetyl-2,3-dideoxy-D-erythro-α-2-hexyl)-delta^5-cholestene with an oxidizing agent to form a first product and then reducing said first product with a metal hydride reducing agent to form a second product.

6. Method according to claim 5, wherein said first product is 3ß-O-(4,6-O-diacetyl-2,3-dideoxy-D-erythro-α-2-hexyl)-delta^5-cholesten-7-one.

7. Method according to claim 5, wherein said second product is 3ß-O-(4,6-dihydroxy-2,3-dideoxy-D-erythro-α-2-hexyl)-delta^5-cholesten-7ß-ol in admixture with 3ß-O-(4,6-dihydroxy-2,3-dideoxy-D-erythro-α-2-hexyl)-delta^5-cholesten-7α-ol.

8. Method according to claim 5, wherein said oxidizing agent is

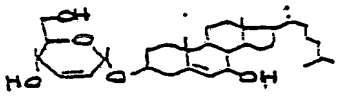
t-butyl-chromate, pyridine-chromium trioxide or pyridine chlorochromate.

9. Method according to claim 5, wherein said reducing agent is $LiAlH_4$ $LiBH_4$, $NaBH_4$ or KBH_4.

10. Method according to claim 7, further comprising separating the 3ß-O-(4,6-dihydroxy-2,3-dideoxy-D-erythro-α-2-hexyl)-delta^5-cholesten-7ß-ol from the 3ß-O-(4,6-dihydroxy-2,3-dideoxy-D-erythro-α-2-hexyl)-delta^5-cholesten-7α-ol.

11. Method according to claim 10, wherein said separated 3ß-O-(4,6-dihydroxy-2,3-dideoxy-D-erythro-α-2-hexyl)-delta^5-cholesten-7ß-ol is processed with a pharmaceutically acceptable carrier to form a pharmaceutical composition.

12. Compound of formula



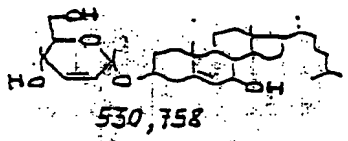
530,758

13. Medicament which comprises a pharmaceutically effective amount of 3ß-O-(4,6-dihydroxy-2,3-dideoxy-D-erythro-α-2-hexyl)-delta^5-cholesten-7ß-ol together with another pharmaceutically acceptable ingredient.

14. Method according to Claim 13, wherein said another ingredient is selected from the group consisting of carriers, preservatives, solubilizers, stabilizers, humectants, emulsifiers, sweetening agents, dyes, scents, salts to modify the osmotic pressure, buffers, coating agents, antioxidants.

15. Medicament according to claim 13, wherein said amount is effective to treat symptoms of at least one member selected from the group consisting of cancer disease, geriatric disease, states of restlessness and states of weakness.

16. Method of treating symptoms of at least one member selected from the group consisting of cancer disease, geriatric disease, states of restlessness and states of weakness, comprising administering to a patient suffering from cancer disease, geriatric disease, states of restlessness as states of weakness a pharmaceutically effective amount of a compound of the formula:



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17. Method according to claim 16, wherein said compound is administered to said patient in admixture with another pharmaceutically acceptable ingredient.

18. Method according to claim 17, wherein said another ingredient is selected from the group consisting of carriers, preservatives, solubilizers, stabilizers, humectants, emulsifiers, sweetening agents, dyes, scents, salts to modify the osmotic pressure, buffers, coating agents, antioxidants.

19. Method according to claim 16, wherein said compound is administered in a form selected from the group consisting of tablets, dragees, pills, gelatin capsules, soft capsules, suppositories, solutions, emulsions, suspensions, injectable solutions, troches, liniments, salves, ointments, creams.

20. A glycoside formed by the process comprising glycosylating

delta^5-cholesten-3ß-ol by reaction with 3,4,6-tri-O-acetyl-D-glucal in the presence of a catalytic amount of molecular iodine to form a first product.

21. A glycoside according to claim 20, wherein said process further comprises oxidizing said first product with t-butyl-chromate to form a second product, reducing said second product with $LiAlH_4$ to form a mixture of glycosides, and isolating from said mixture of glycosides a glycoside which includes a 7ß-ol moiety.

22. A glycosidic vinyl ether of an hydroxy compound selected from the group containing cholesterols, bile salts, steroid hormones, and vitamin D compounds.

23. A glycosidic vinyl ether according to claim 22 wherein the hydroxy compound is selected from the group containing cholic acid and derivatives, 25-hydroxy-cholesterol, 25-hydroxy-calciferol, Pregnenolone, 17α-hydroxy-pregnenolone, 17α-hydroxy-progesterone, 11-desoxy-corticosteron, 11-desoxy-cortisol, corticosterone, cortisol, cortisone, androsterone, testosterone, estrone, 17ß-estradiol, estratriol-3, 16α, 17ß, 3α, 5ß-tetrahydro-corticosterone, urocortisol and allocortolone.

24. A method according to claim 1, wherein said member is an hydroxy-steroid and wherein said hydroxy-steroid is selected from the group containing cholic acid and derivatives, 25-hydroxy-cholesterol, 25-hydroxy-calciferol, Pregnenolone, 17α-hydroxy-pregnenolone, 17α-hydroxy-progesterone, 11-desoxy-corticosteron, 11-desoxy-cortisol, corticosterone, cortisol, cortisone, androsterone, testosterone, estrone, 17ß-estradiol, estratriol-3, 16α, 17ß, 3α, 5ß-tetrahydro-corticosterone, urocortisol and allocortolone.

Diagram 1

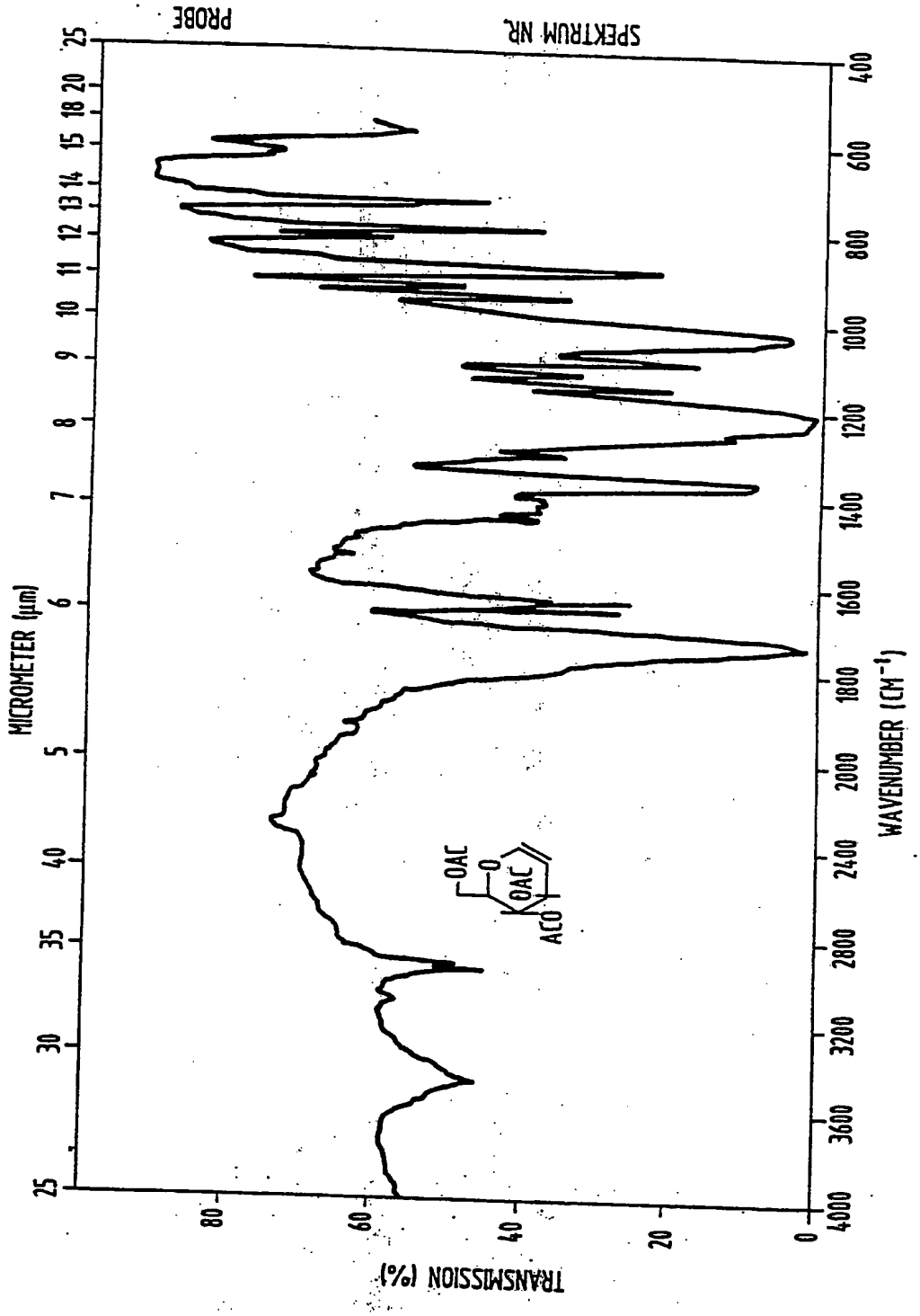

PROBE
SPEKTRUM NR.
MICROMETER (µm)
WAVENUMBER (CM⁻¹)
TRANSMISSION (%)
OAc
O
OAc
AcO

Diagram 2

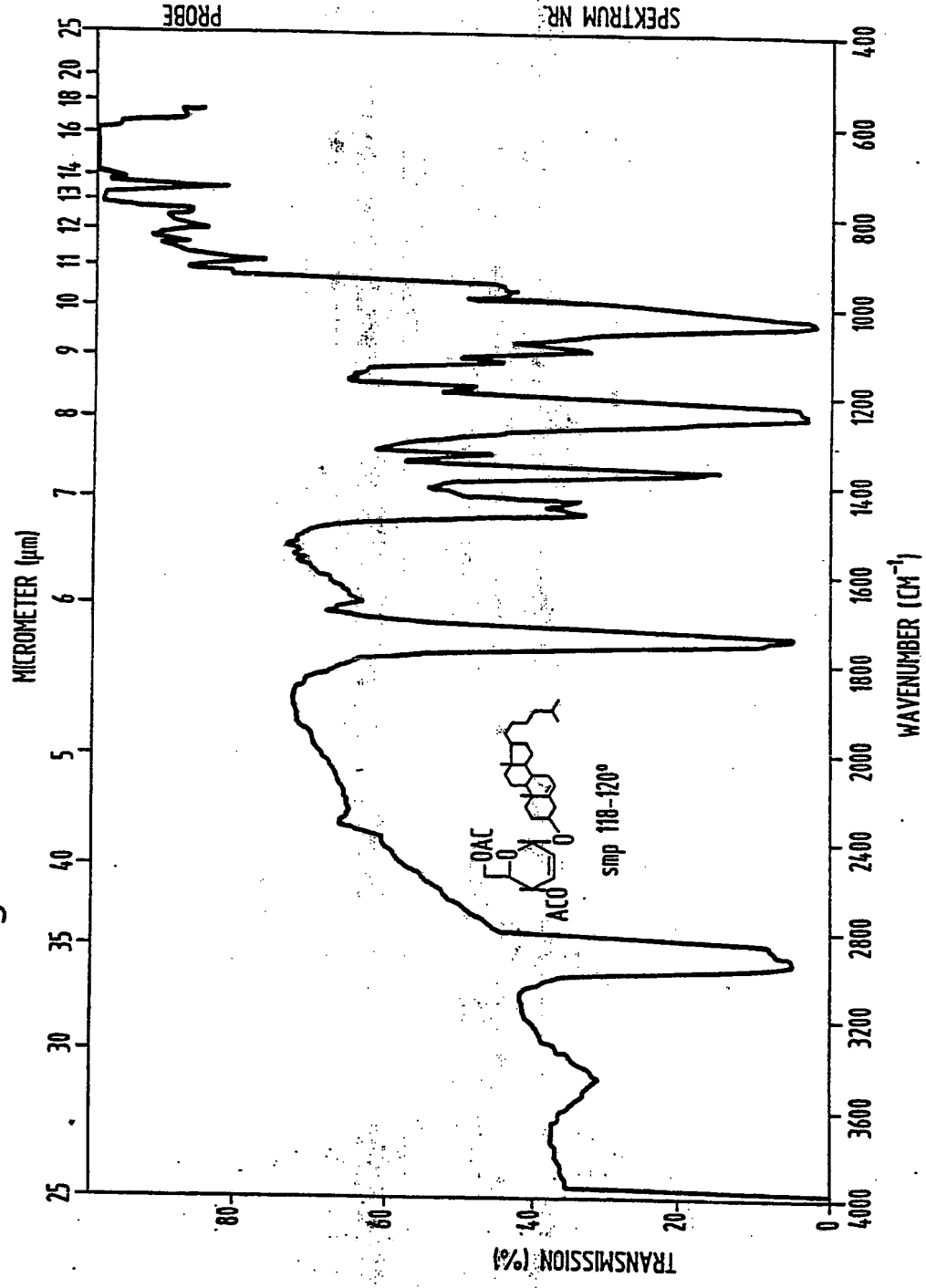

PROBE
SPEKTRUM NR.
MICROMETER (µm)
WAVENUMBER (CM⁻¹)
TRANSMISSION (%)
OAC
ACO
smp 118-120°

Diagram 3

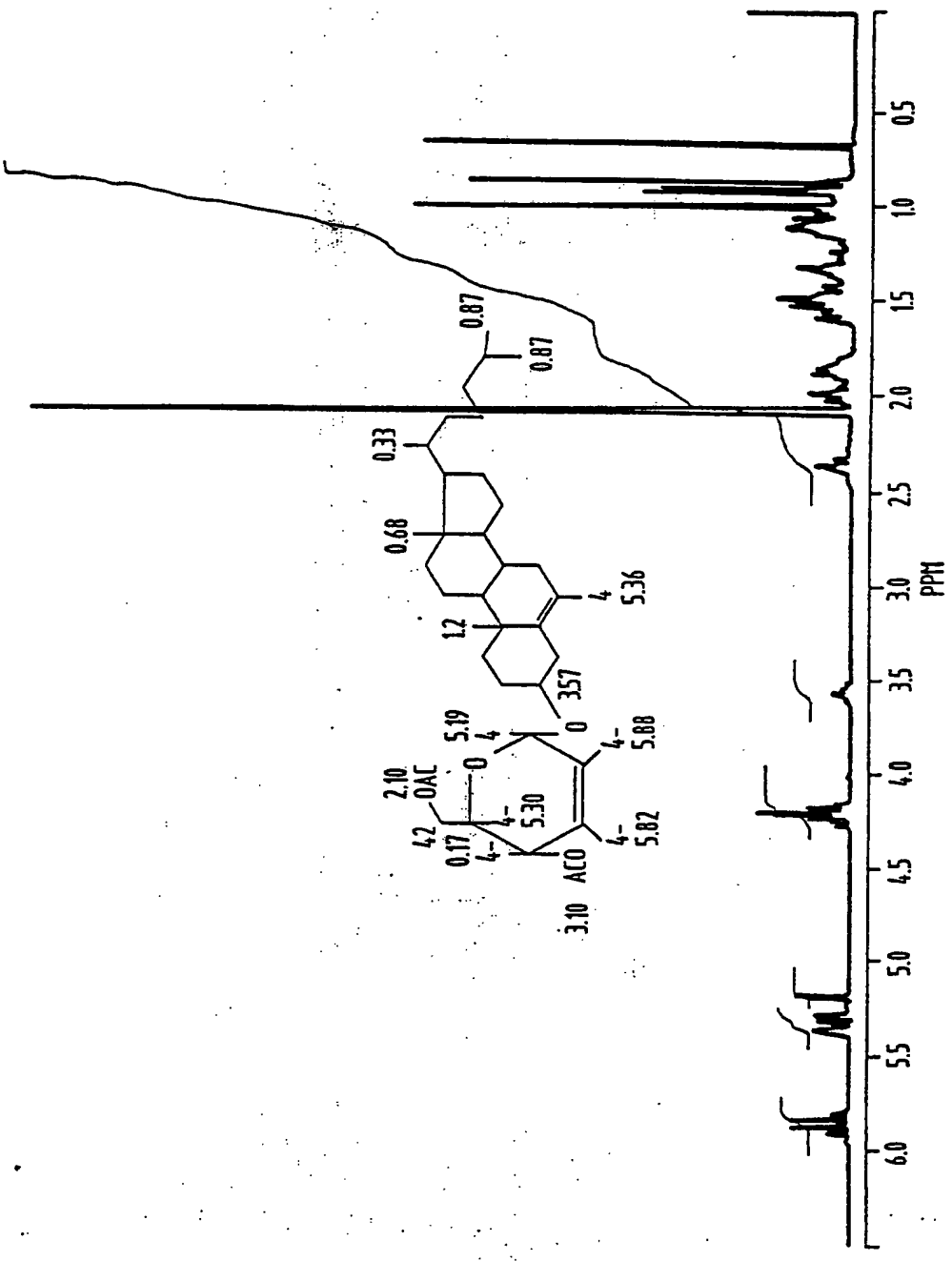

0.87
0.87
0.33
0.68
1.2
4
5.36
357
0
5.19
4
4-
5.88
2.10
OAC
0
4-
5.30
42
0.17
4-
4-
5.82
3.10
ACO
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
PPM

Diagram 4

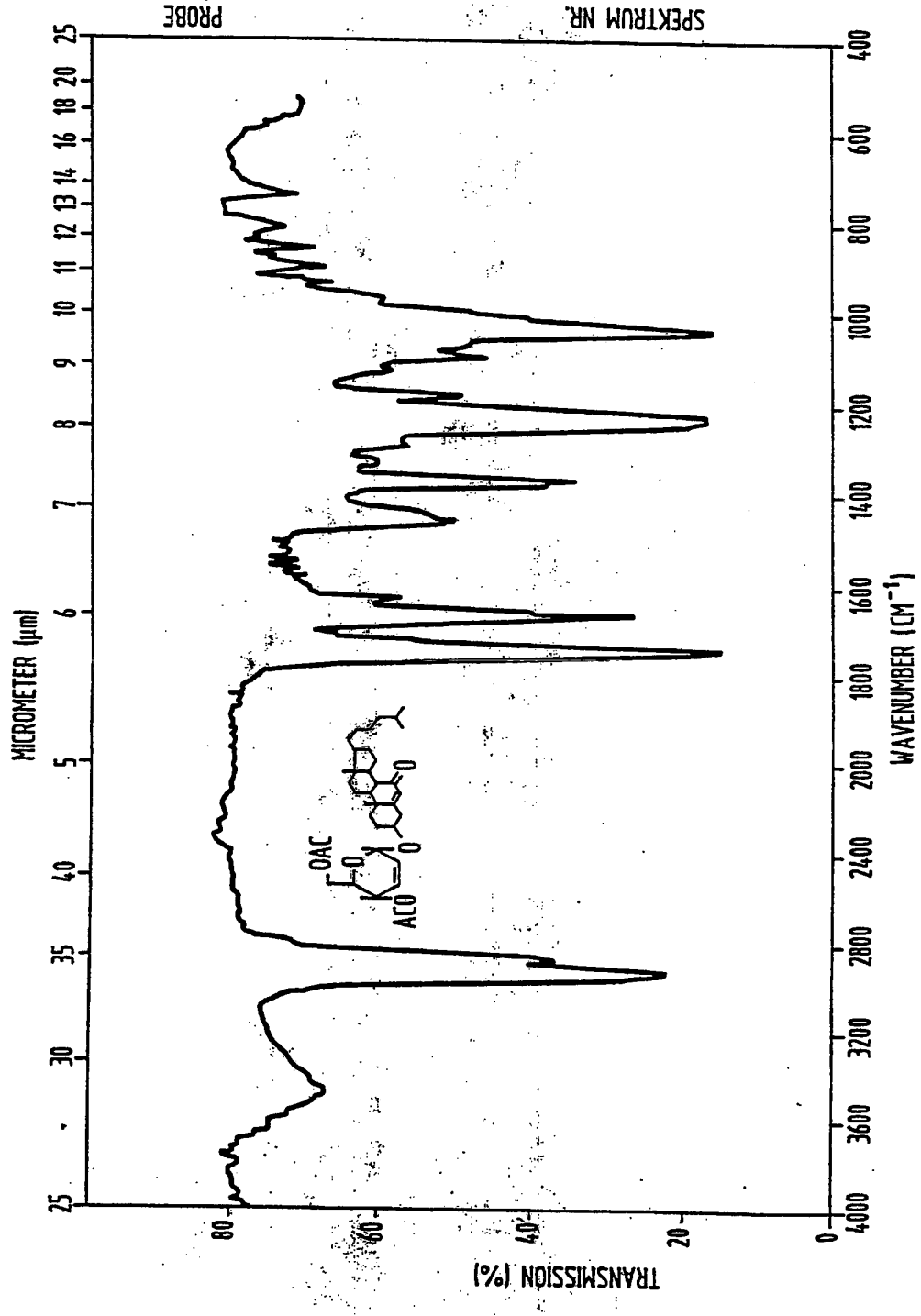

PROBE
SPEKTRUM NR.
MICROMETER (µm)
WAVENUMBER (CM⁻¹)
TRANSMISSION (%)
OAC
ACO
O

Diagram 5

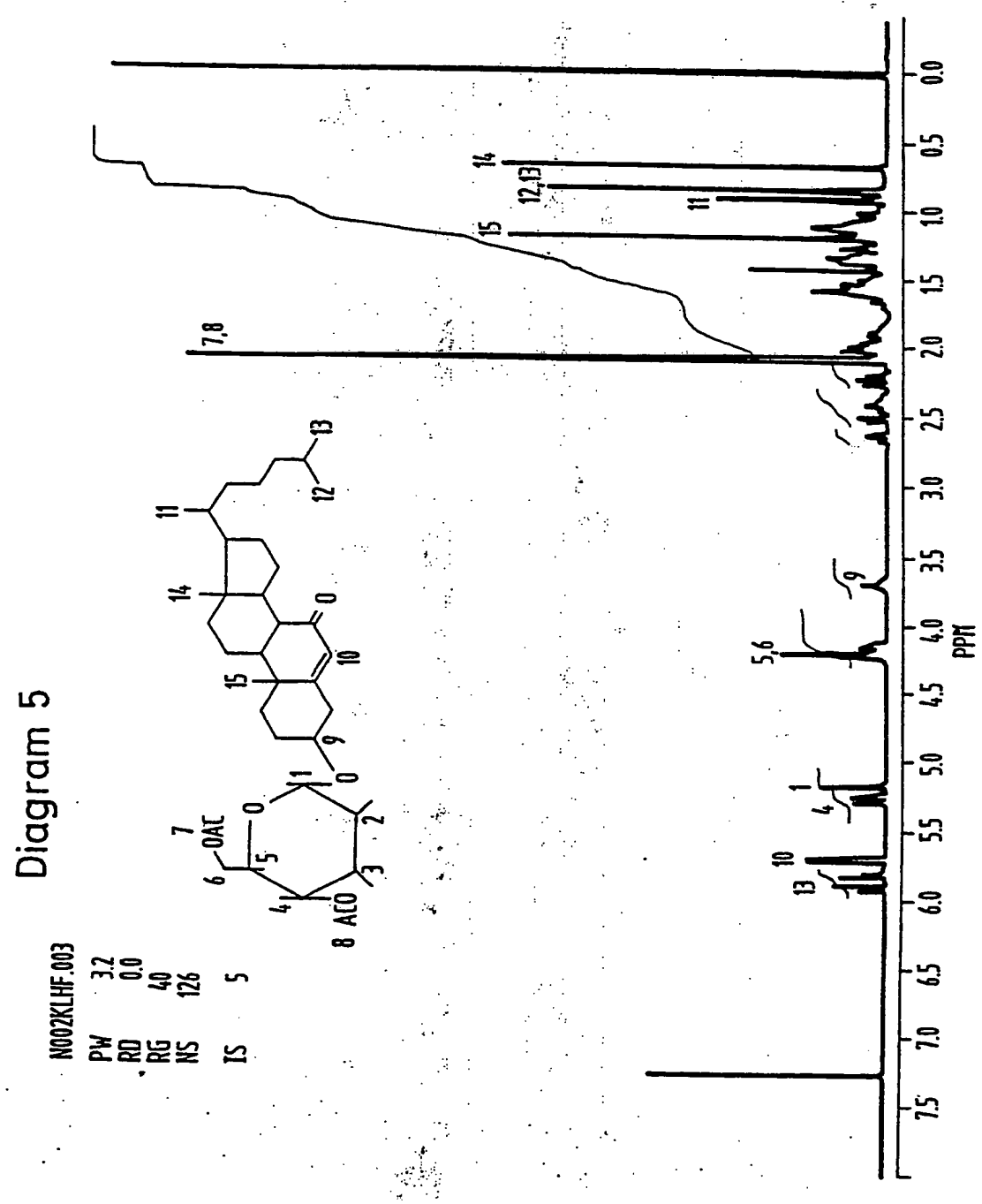

N002KLHF.003
PW 3.2
RD 0.0
RG 40
NS 126
IS 5
OAc
AcO
7,8
14
15
12,13
11
5,6
9
1
4
10
13
PPM

Diagram 6

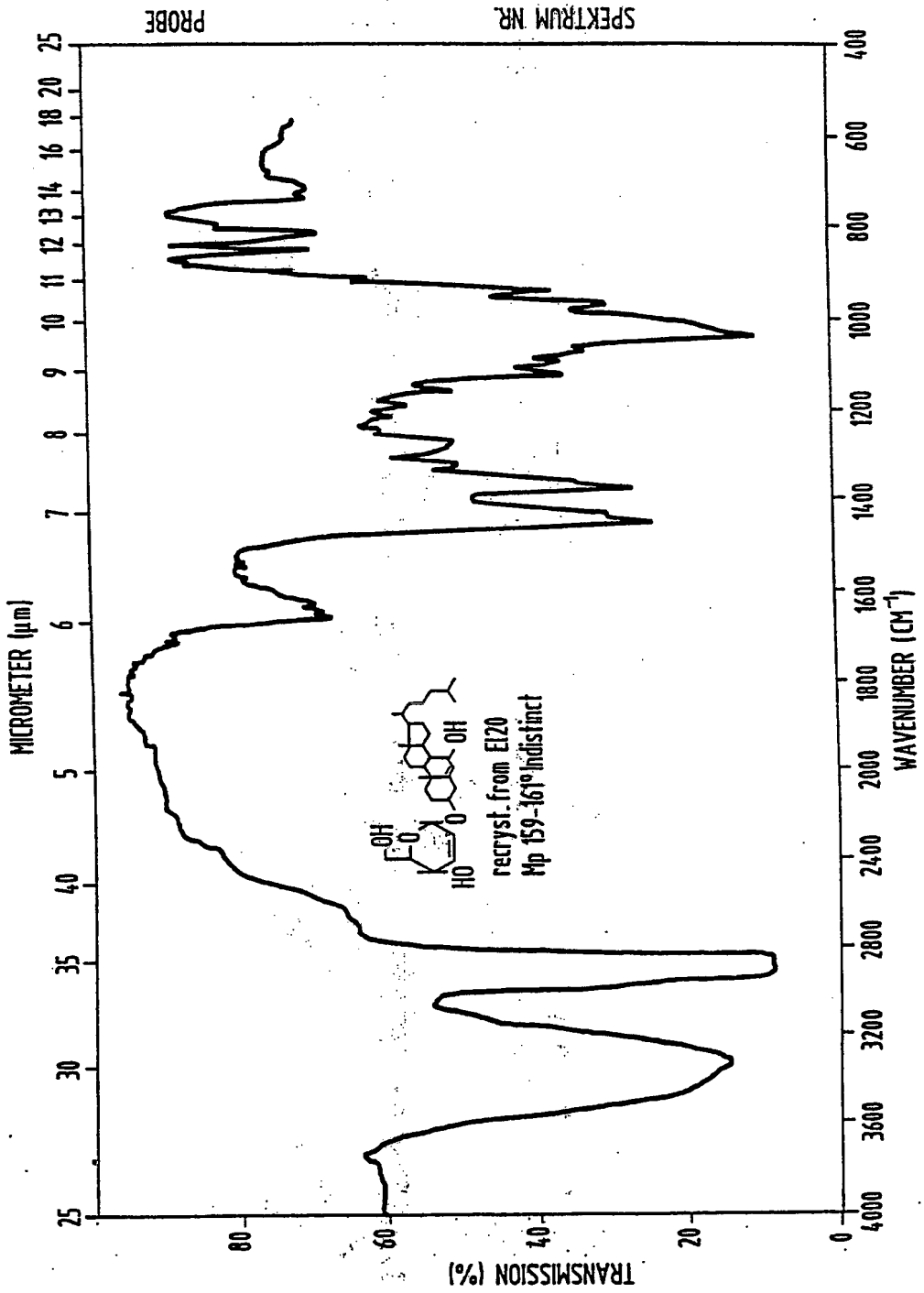
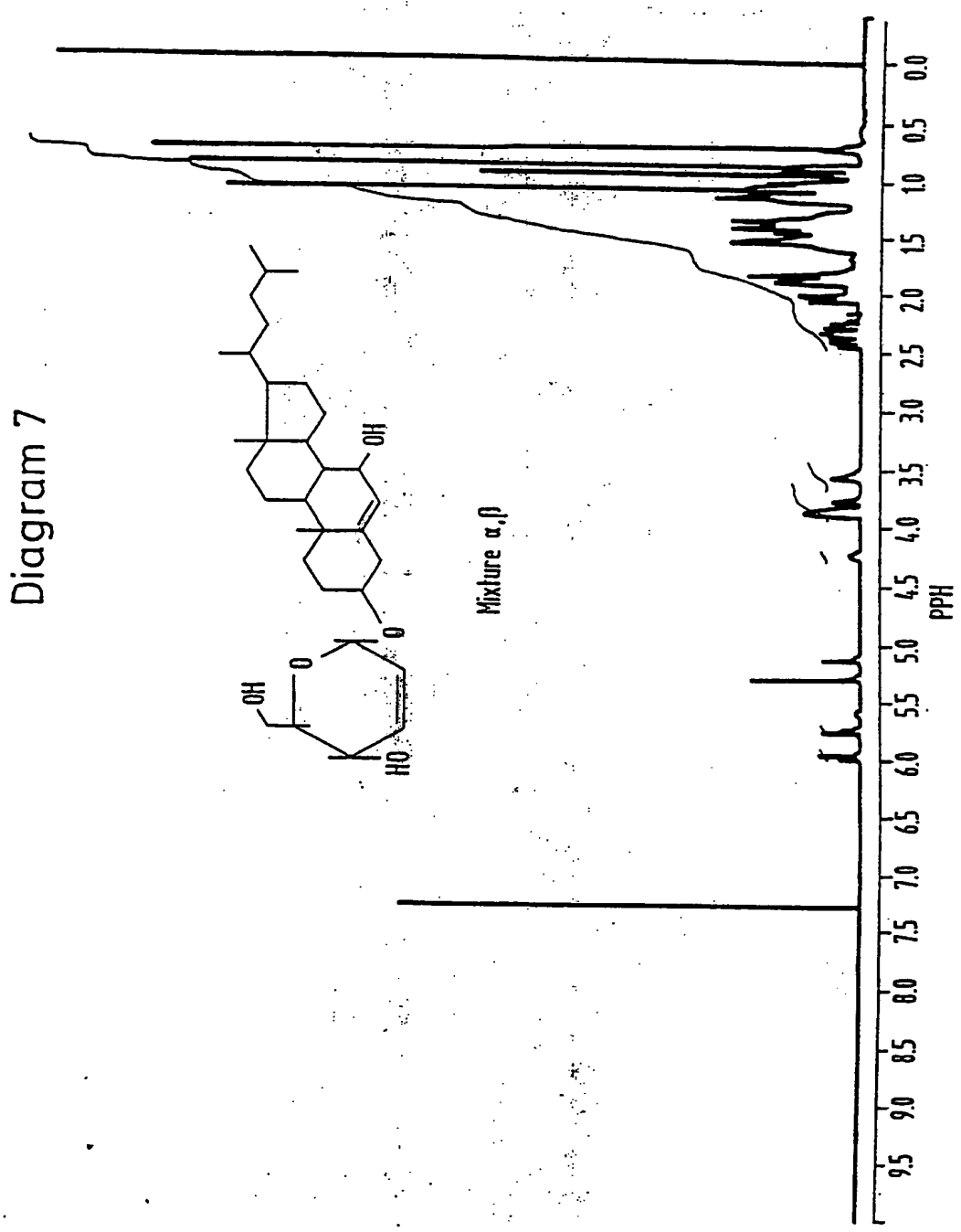

PROBE
SPEKTRUM NR.
MICROMETER (µm)
WAVENUMBER (CM⁻¹)
TRANSMISSION (%)
recryst. from Et2O
Mp 159-161° indistinct

Diagram 7


OH
O
O
OH
HO
Mixture α,β
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
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6.0
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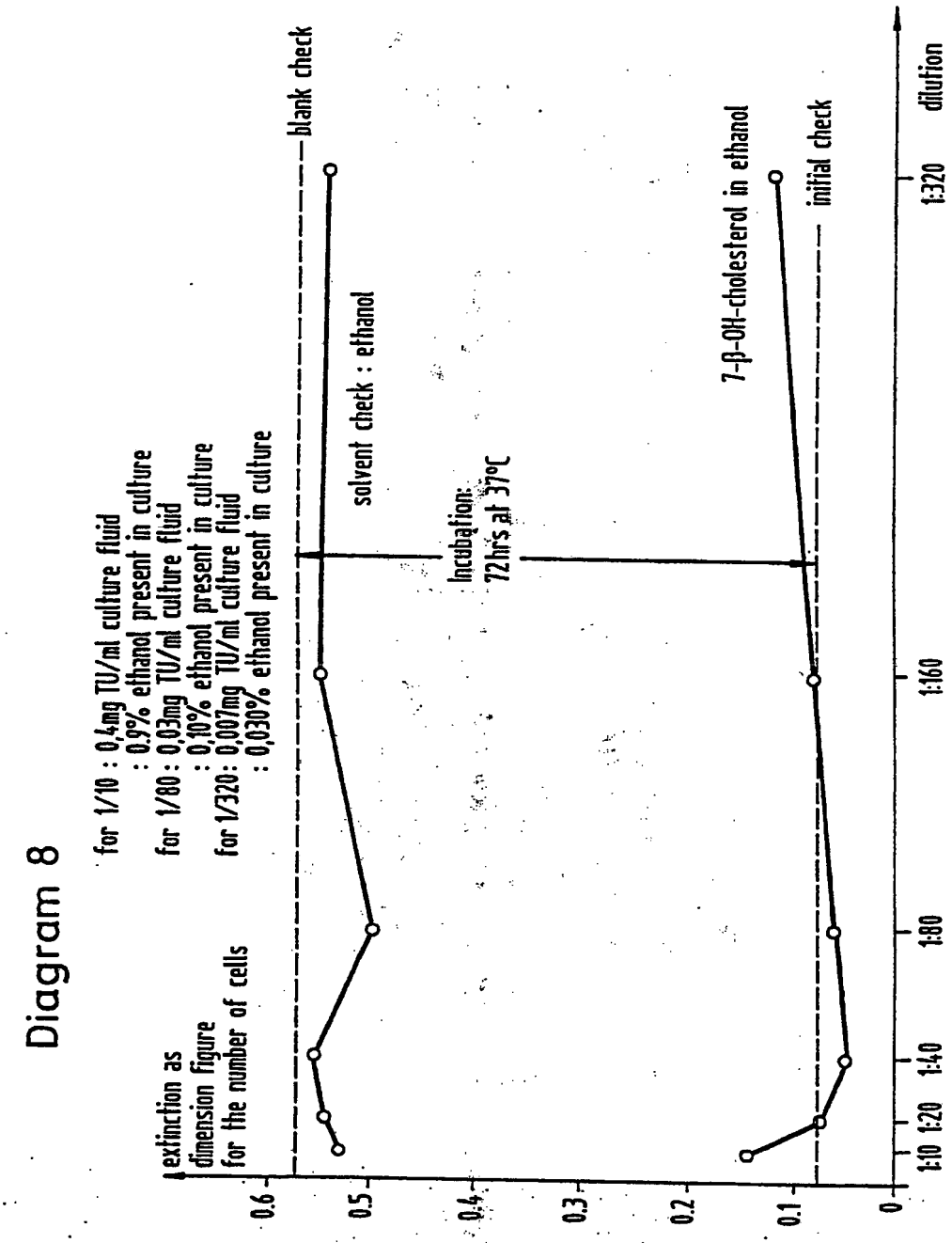
7.5
8.0
8.5
9.0
9.5
PPM



INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/00115

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 J 17/00, A 61 K 31/58

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 J 17/00, A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [9]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	Liebigs Annalen der Chemie 1985, VCH Verlagsgesellschaft mbH, (Weinheim, DE), J. Thiem et al.: "Untersuchungen zur Darstellung von Desoxyzucker-Steroid-glycosiden", pages 2135-2150 see the whole article	22,23
A	--	1,2
X	FR, A, 2007410 (FARBWERKE HOECHST AG) 9 January 1970 see the whole document	22
A	--	1
A	DE, A, 3127933 (BASF AG) 8 April 1982 see page 8, compound (d)	10
	--	
	./.	

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
20th March 1991	25. 04. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	F.W. HECK

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	Carbohydrate Research, vol. 29, no. 2, August 1973, (Amsterdam, NL), S. Honda et al.: "Preparation of O-(2-deoxy-α-D-arabino-hexopyranosyl)-(1→6)-D-glucose by the oxiodination-hydrogenation method", pages 488-491 see the whole article	1
A	Carbohydrate Research, vol. 92, 1981, Elsevier Scientific Publishing Co., (Amsterdam, NL), P.J. Garegg et al.: "Novel glycosylation reagents: synthesis of disaccharides containing 2-deoxy-2-iodo-α-D-talopyranosyl groups", pages 157-159 see the whole article	1

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers XX, because they relate to subject matter not required to be searched by this Authority, namely:

xx Claims 16-19

Pls. see Rule 39.1 (iv) PCT:

Method for treatment of the human or animal body by surgery or therapy as well as diagnostic methods.

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9100115 SA 43965

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 12/04/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A- 2007410	09-01-70	AT-A- 292928	15-08-71
		BE-A- 731175	08-10-69
		CH-A- 550158	14-06-74
		DE-A,B 1768165	14-10-71
		GB-A- 1268230	22-03-72
		NL-A- 6904759	08-10-69
		US-A- 3642770	15-02-72
DE-A- 3127933	08-04-82	None	